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(54) Title: PROCESS FOR IMPROVING FLOW AND COMPRESSION OF TABLETING COMPOSITIONS

(57) Abstract

A method of forming a flowable tablet blend having cohesive properties comprising, mixing a shearform matrix and a binder, densifying said mixture to uniformly localize said binder into said uncured shearform matrix and form a compacted mass, and sizing said compacted mass to form flowable particles of a blend. Tablets made from such blends are disclosed herein.

PROCESS FOR IMPROVING FLOW AND COMPRESSION OF TABLETING COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to flowable tabletable compositions formed from shearform matrices which have cohesive properties due to the use therein of specific ingredients and subjecting some to certain process conditions. Chewable products can be made using these compositions and methods.

RELATED APPLICATIONS

This application is a continuation-in-part of application Serial No. 08/914,972, filed August 20, 1997.

BACKGROUND OF THE INVENTION

Matrices formed by flash-flow processing are well known. For example, U.S. Patents 5,380,473 and 5,429,836, incorporated herein by reference, describe the flash-flow process and the formation of amorphous solid shearform matrices.

The use of amorphous shearform matrices for forming dosage units has been described in co-assigned and co-pending PCT Application No. PCT/US95/07144, filed June 6, 1995. This application discloses a quick dissolving tablet which is formed using flash-flow technology to provide a shearform matrix.

Co-pending and co-assigned PCT Application No. PCT/US95/07194, filed June 6, 1995 also discloses a process and apparatus for making rapidly dissolving dosage units such as tablets by flash-flow processing.

Cohesiveness and binding properties are critical to compositions intended to be used for discrete dosage units, such as tablets. Binding additives, such as glycerine, have been used in flash-flow matrices to provide self-binding properties. The addition of glycerine renders the shearform matrix cohesive and serves to bind the structure together. U.S.S.N. 08/914,972, filed August 20, 1997, discusses the use of added glycerine. Its disclosure is hereby incorporated by reference. The use of glycerine in the matrix has its

disadvantages, however, in that processing of such matrices in conventional tableting machinery has been difficult due to sticking of the composition to the tableting equipment and due to poor flow of the composition through the equipment.

Recently, it was discovered that similar cohesive and self-binding properties can be attained by including certain sugar alcohols in the feedstocks for shearform matrices. See U.S. Applications 08/915,068 and 08/915,067, both filed on August 20, 1997, and both incorporated by reference. However, there are processing problems associated with these matrices too.

The present invention uses unique materials and processing means to address the problems encountered when tableting shearform matrices containing added binding materials, such as glycerine, or those made from sugar alcohol ingredients.

Flash-flow processing typically begins with solid starting materials. The original material then undergoes an instantaneous change during flash flow processing. The resultant amorphous material, generally a floss, has a different morphology and structure than the original material. The use of added glycerine or cohesivity enhancing ingredients in the floss component of tableting composition has generally precluded the use of conventional high speed tableting processes. Thus, there is a need for a method of effectively dealing with shearform compositions and matrices containing binding materials or certain ingredients which provide binding and cohesive properties, but which render them unusable in conventional tableting machinery and processes.

SUMMARY OF THE INVENTION

The invention is concerned with flowable tabletable compositions and with rapid dissolve and chewable products made therefrom. The overall procedure by which products are made using the invention involves three essential steps:

(1) preparing a cohesive, free-flowing tabletable composition based upon a shearform matrix and containing at least one bio-affecting agent, at least one crystallization modifier, and employing at least one of: (a) a binding additive, and (b) a sugar alcohol ingredient;

(2) densifying and milling that composition; and

(3) compressing it to form tablets.

Other techniques, e.g., drying and sieving steps, can be used at various points in the overall procedure.

Useful bio-affecting agents are discussed hereinbelow. Antacid agents, e.g., calcium carbonate, vitamins, e.g., Vitamins C and D, and NSAID s, e.g., ibuprofen, acetominaphin and mixtures containing same are among the preferred bio-affecting agents.

The tabletable compositions used in step (1) are produced via the use of one or both of (a) a binding additive and (b) particular component(s) in the matrix.

The binding additive (a) of the invention is generally added to the matrix after it is produced. Useful additives include water, glycerine, sorbitol, mannitol, xylitol and the like, with glycerine preferred. Mixtures can be used.

The ingredients (b) which can be employed in making matrices in accordance with the invention include certain sugar alcohols and other substances which tend to lend hygroscopic properties to the matrix produced therefrom. Among these are maltitol, mannitol, sorbitol and xylitol. Xylitol and sorbitol are preferred floss components.

After the floss is made it may be treated with one or more crytallization modifiers, eg., ethanol and one or more glidants, eg., lactose. It is usually chopped before compression.

The treated floss is then compressed. The compression step includes shaping the densified and milled formulations to yield tablets whose surfaces are tailored to be readily fractured during chewing. These chewable tablets typically have hardness values of about 6.0 to 30.0 pounds (i.e., 3.0 to 15.0 SCU's), preferably about 10 to about 12 pounds.

The process of the present invention permits the use of shearform matrices which are highly hygroscopic and inclined to transform from their amorphous state to a recrystallized state. The ability to use binding materials, such as binding additives and/or sugar alcohol constituent(s) allows shearform matrices to be used to produce tablets at both low and high pressures, *i.e.,* under 500 psi and up to 8,000 psi, which tablets have excellent structural integrity, yet also exhibit exceptional dissolution characteristics as compared to conventional tablets. The ability to dissolve rapidly when placed in the mouth is of great importance to the pharmaceutical industry, especially where patient

compliance is of concern. Rapidly dissolving tablets are difficult to manufacture, especially on commercial high speed tableting equipment, because the compression forces required to produce a high quality tablet are often so high that the decreased tablet porosity does not permit rapid penetration of fluids. Additionally, tableting formulations often require various tableting excipients such as lubricants, flow aids, glidants and the like, which help the formulations flow into the tablet dies and which also help produce quality tablets of the requisite density and hardness. These materials, however, can also affect dissolution rates.

Applicants have discovered that when they subject a substantially amorphous composition containing a shearform matrix made with either (a) a binding material, or (b) sugar alcohol constituent(s), to a compaction and densification process prior to tableting, the resultant amorphous shearform matrix loses its surface stickiness.

As a result of the compaction of a glycerine treated shearform matrix, the glycerine is uniformly distributed throughout the matrix, then occluded from the surface and internalized in the amorphous matrix carrier to become densified therein.

Alternatively, shearform matrices made from feedstocks containing one or more of certain sugar alcohols -- with optional subsequent treatment with binding additives -- are mixed with conventional pharmaceutical ingredients, then compacted and densified.

The densified mass is then milled to form particles which are free flowing, yet cohesive and self-binding when subjected to tableting forces. Tablets made from such free flowing particles using conventional tableting machinery, e.g. at about 1,500 to about 8,000 psi, exhibit dissolution at extremely rapid rates when placed in the mouth and optionally chewed. Typically, the tablets dissolve within 30 seconds or less, preferably 20 seconds or less.

Without wishing to be bound by any one theory, it is believed that by applying appropriate compaction forces on a suitable tableting composition containing matrix particles prior to tableting, any liquid binder present is forced into the interstices of the matrix fiber network, where it remains. Once any liquid binder material is forced to penetrate the floss network and become sorbed therein, it is effectively removed from the exposed floss surface, causing floss particles formed from the subsequent milling step to

be free flowing.

If compositions on sugar alcohol-containing matrices are treated in the absence of liquid binder(s), the compacting and densifying steps serve to eliminate much of the floss' "stickiness" and make milled floss particles free flowing.

The resultant particles of tableting composition are suitable for use in conventional tableting equipment because they are free flowing and resist sticking. Yet compositions containing these free flowing particles retain their ability to form a cohesive tablet by virtue of the binder additives which reside within the granules and/or are constituents of the matrix particles. The matrix particles then function to bind adjacent particles together under the compression forces of tableting.

In one embodiment of the invention, there is provided a method of forming a flowable feedstock having cohesive properties. The method includes providing a mixture of shearform matrix and a binding additive, the combination of which would ordinarily be difficult to process using conventional tableting equipment due to the sticking and/or resistance to the flow of the composition in the tableting equipment. The mixture of shearform matrix and binding additive is then densified to uniformly localize the binding material into the matrix and to form a compacted mass therefrom. This mass is then milled to form flowable particles. Once the tableting composition has been subjected to these processing steps, it can be used in conventional commercially available tableting equipment, i.e., high speed tableting equipment, without concerns for sticking, blocking or other similar disadvantages traditionally encountered with such shearform compositions.

In another embodiment, there is provided a method of converting a mixture having self-agglomerating properties into a blend having free flowing properties. The matrix particles therein contain one or more sugar alcohols, e.g., xylitol. This method includes compacting a mixture of self-agglomerating matrix particles, bio-affecting agent, crystallization modifier, and binding additive, to form a compacted mass. This compacted mass is then milled to form a free flowing particulate blend. Once the free flowing particulate blend has been formed, it can be incorporated into a tableting composition and used in conventional tableting equipment without encountering the

sticking and/or flow concerns of the same compositions which have not been subjected to the above-mentioned process steps.

In still another embodiment of the present invention, there is contemplated a free flowing particulate feedstock blend formed from a self-agglomerating, sticky mixture of shearform matrix and binder, said self-agglomerating mixture having been subjected to compaction to form a compacted mass and subsequently to sizing of said compacted mass to form said free flowing particulate feedstock blend.

The shearform matrices used herein are based upon carriers selected from the group consisting of: monosaccharides, disaccharides, polydextrose, maltodextrin, oligosaccharides and mixtures thereof. Mono- and disaccharides, such as sugars, are generally used as carriers.

The binding additives useful in the present invention include water, glycerine, xylitol, sorbitol, mannitol and combinations thereof, as well as other materials which are useful in providing cohesiveness and binding due to the stickiness they naturally impart to the carrier component. Amounts of about 1.0 to about 5.0% are useful. Glycerine is the preferred binding additive.

The feedstock ingredients which function as binding materials are one or more of xylitol, sorbitol and mannitol. Xylitol and sorbitol, and combinations thereof, are preferred floss constituents. Combinations in which the ratio of sorbitol to xylitol is about 1:0.1 to 1:1.0 are preferred combinations. Mannitol, sorbitol or xylitol can be used alone.

The processes of the present invention focus on one or more of: (a) uniformly localizing the binding additive(s) under the surface of particles in the uncured shearform matrix, causing the stickiness associated with the binder to be entrapped within the matrix mass, leaving the surface substantially free of sticky character; and (b) treating an uncured shearform matrix, produced from a feedstock containing xylitol, sorbitol and/or mannitol to compact and densify it and eliminate stickiness.

Suitably compacted/densified feedstocks are in the form of free flowing particles having self-binding and cohesive properties such that useful tableting compositions can be made therefrom. The free flowing particles formed in the present invention can be

processed on conventional tableting equipment, i.e. using high speeds and ambient conditions.

DETAILED DESCRIPTION OF THE INVENTION

The invention involves novel compositions and processes for preparing bioaffecting products. Unless stated otherwise, all percentages recited are weight percentages, based on total composition weight.

Compositions

The compositions of the invention employ shearform matrix particles made using either or both of (a) a binding additive and (b) a sugar alcohol constituent.

The matrix particles are produced from feedstocks containing one or more saccharides. While simple sugars, e.g., sucrose, are preferred constituents, other ingredients, such as polydextrose can be used in the feedstock.

In addition, the self-binding and cohesive properties of the tablet formulations herein are augmented by the use of at least one sugar alcohol as a constituent of the feedstock from which the matrix is made. Maltitol, mannitol, sorbitol and xylitol can be used, with sorbitol and xylitol preferred. Generally, one or more of the cohesivity enhancing sugar alcohols are used at concentrations of about 10% or more, with amounts of about 10% to about 50% of the feedstock being useful.

The matrix feedstock may optionally include one or more conventional pharmaceutical and/or tabletting additives. One preferred additive is Polysorbate 80, ("TWEEN 80"), a surfactant.

In addition to bioaffecting agent(s) and crystallization modifier(s) described infra, the tablet compositions contain optional binding additives, preferably glycerine, in amount of about 0.5% to about 20%, preferably 0.5% to 5%.

Tableting compositions might employ bioaffecting agents, such as pharmaceutical agents and the like, which are preferably added in the form of uniform microspheres. The apparatus and procedures for forming microspheres of active agents is described in U.S. patent 5,683,720, which is incorporated herein by reference.

The active ingredients useful herein can be selected from a large group of therapeutic agents. Respective classes include those in the following therapeutic

categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal drugs; anti-allergy agents; anti-arrhythmia agents; antiasthmatics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatories; antilipid agents; antimanics; anti-migraine agents; antinauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antiobesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antiulcer agents; anti-uricemic agents; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

Active agents which may be used in the invention include: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; astemizole; atenolol; azatidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone diproprionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride; bethanechol; biotin; bisacodyl; bismuth subsalicylate; bornyl acetate; bromopheniramine and its maleate; buspirone; caffeine;

calamine; calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; centrizine and its hydrochloride; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine and its maleates and tannates; chlorpromazine; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine and its hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine and its hydrochloride salt; clorfibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine and its hyddrochloride; danthron; dexbromopheniramine maleate; dextromethorphan and its hydrohalides; diazepam; dibucaine; dichloralphenazone; diclofen and its alkali metal sales; diclofenac sodium; digoxin; dihydroergotamine and its hydrogenates/mesylates; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali metal salts; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; dronabinol; efaroxan; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fluoxetine; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine and its hydrochloride; flurbiprofen; furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron and its hydrochloride; griseofulvin; growth hormone; guafenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; loratadine; lovastatin; luteinizing hormore; LHRH (lutenizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; meclizine and its hyddrochloride; mefenamic acid; meclofenamic acid; meclofenamate sodium;

medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methscopolamine and its nitrates; methsergide and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide; metoclopramide and its halides/hydrates; metronidazole and its hydrochloride; metoprotol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nimesulide; nitroglycerine; nonoxynol-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondansetron and its hydrochloride; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-O; paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium; perphenazine; phenelzine sulfate; phenindamine and its tartrate; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and hydrochlorides; phenylpropanolamine and its hydrochloride salt; phenytoin; pirmenol; piroxicam and its salts; polymicin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; promethazine and its hydrochloride; propoxyphene and its hydrochloride and napsylate; pramiracetin; pramoxine and its hydrochloride salt; prochlorperazine and its maleate; propanolol and its hydrochloride; promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and hydrochorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinapril; quinidine gluconate and sulfate; quinestrol; ralitoline; ranitadine; resorcinol; riboflavin; salicylic acid; scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole; sulfasalazine; sulfur; sumatriptan and its succinate; tacrine and its hydrochloride; theophylline; terfenadine; thiethylperazine and its maleate; timolol and its maleate; thioperidone; tramadol; trimetrexate; triazolam; tretinoin; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride; tripelennamine and its hydrochloride; tripolidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B_1, B_2, B_6, B_{12}, E, and K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate.

Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

Particularly useful active agents include H_2 antagonists, analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), anticholestero- lemics, anti-allergy agents, and anti-migraine agents.

Analgesics include aspirin, acetaminophen, acetaminophen plus caffeine, and non-steroidal anti-inflammatory drugs (NSAIDS), *e.g.,* ibuprofen and nimesulide.

Useful NSAIDs include ibuprofen; diclofenac and its alkali metal salts; fenoprofen and its metal salts; fluriprofen; ketoprofen; naproxen and its alkali metal salts; nimesulide; and piroxicam and its salts.

H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Useful anti-allergy agents include hydricodone and its tartrates; clemastine and its fumarate; azatadine and its maleate; acetaminophen; hydroxyzine and its pamoate and hydrochloride salts; chlorpheniramine and its maleates and tannates; pseudoephedrine and its sulfates and hydrochlorides; bromopheniramine and its maleate; dextromethorphan and its hydrohalides; loratadine; phenylephrine and its tannates and hydrochlorides; methscopolamine and its nitrates; phenylpropanolamine and its hydrochlorides; codeine and its hydrochloride; codeine and its phosphate; terfenadine; acrivastine; astemizole; cetrizine and its hydrochloride; phenindamine and its tartrate; tripelennamine and its hydrochloride; cyproheptadine and its hydrochloride; promethazine and its hydrochloride; and pyrilamine and its hydrochlorides and tannates.

Useful antimigraine agents include divalproex and its alkali metal salts; timolol and its maleate; propanolol and its hydrohalides; ergotamine and its tartrate; caffeine; sumatriptan and its succinate; dihydroergotamine, its hydrogenates/mesylates; methsergide and its maleate; isometheptene mucate; and dichloralphenazone.

Another class of drugs which can be used are antiemetics. Useful antiemetics include: meclizine and its hydrochloride; hydroxyzine and its hydrochloride and pamoate; diphenhydramine and its hydrochloride; prochlorperazine and its maleate; benzquinamide and its hydrochloride; granisetron and its hydrochloride; dronabinol;

bismuth subsalicylate; promethazine and its hydrochloride; metoclopramide and its halides/hydrates; chlorpromazine; trimethobenzamide and its hydrochloride; thiethylperazine and its maleate; scopolamine; perphenazine; and ondansetron and its hydrochloride.

Other active ingredients for use in the present invention include antidiarrheals, such as Immodium AD, antihistamines, antitussives, decongestants, vitamins, and breath freshners. Also contemplated for use herein are anxiolytics such as Xanax; antipsychotics such as Clozaril and Haldon; antihistamines such as Seldane, Hismanal, Relafen, and Tavist; antiemetics such as Kytril and Cesamet; bronchodilators such as Bentolin, Proventil; antidepressants such as Prozac, Zoloft, and Paxil; antimigranes such as Imigran, ACE-inhibitors such as Vasotec, Capoten and Zestril; Anti-Alzheimers agents such as Nicergoline; and Ca^{II}-Antagonists such as Procardia, Adalat, and Calan.

Among the anticholesterolemics, the statins, *e.g.,* lovastatin, provastatin and the like are notable.

Combinations of various types of drugs, as well as combinations of individual drugs, are contemplated.

Other ingredients which may be included are flavors, fragrances, dyes, sweeteners both artificial and natural, and other additives.

For example, fillers may be used to increase the bulk of the tablet. Some of the commonly used fillers are calcium sulfate, both di- and tri basic, starch, calcium carbonate, microcrystalline cellulose, modified starches, lactose, sucrose, mannitol, and sorbitol.

Other materials which can be incorporated into the feedstock to enhance the shearform matrix include flavors and sweeteners.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents include volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins and extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other

fruit flavors.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral, i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanal (green fruit), and 2-dodecenal (citrus, mandarin), mixtures thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and mixtures thereof (when not used as a carrier); saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof. Other sweeteners may also be used.

Conventional tableting aids may be selected from a wide variety of materials such as lubricants, glidants, solubility enhancers, crystallization aids, auxiliary binders, anti-caking agents and flow agents. They are present in amounts ranging from about 0% to about 50%, based upon tablet composition weight.

For example, lubricants such as magnesium stearate calcium stearate, zinc stearate, hydrogenated vegetable oils, sterotex, polyoxyethylene, glyceryl monostearate, talc, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, sodium stearyl fumarate, adipic acid, light mineral oil and the like may be employed, with sodium stearyl fumarate preferred. Waxy fatty acid esters, such as glyceryl behenate, sold as "Compritol" products, can be used. Mixtures are operable.

Glidants such as starch, talc, lactose, stearates, dibasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, Cabosil, Syloid, and silicon dioxide may be employed. The use of lactose at about 0.1% to about 2.0% is prefered.

Other useful tableting aids include solubility enhancers, such as the polyethylene glycol-32 (PEG-32) glyceryl ester sold as "Gelucire".

The present invention also contemplates the use of crystallization modifiers, with surfactants and ethanol being preferred crystallization modifiers. Other materials which are non-saccharide hydrophilic organic materials, e.g., ethanol, may also be used. Useful modifiers preferably have a hydrophilic to lipid balance (HLB) of about 6 or more. Such materials include, without limitation, anionic, cationic, and zwitterionic surfactants as well as neutral materials with suitable HLB values. Hydrophilic materials having polyethylene oxide linkages are effective. Those with molecular weights of at least about 200, preferably at least 400, are highly useful.

Crystallization modifiers useful herein include: ethanol, lecithin, polyethylene glycol (PEG), propylene glycol (PG), dextrose, the Spans and Tweens which are commercially available from ICI America, and the surface active agents known as "Carbowax". Generally, the polyoxyethylene sorbitan fatty acid esters called Tweens, or combinations of such modifiers are used. Crystallization modifiers are usually incorporated into matrices in amounts of between about 0% and 10%.

When ethanol is used, it is contacted with the matrix particles in amounts ranging from about 0.5% to about 10%, based on total matrix weight. The particles are then dried and further processed.

Other ingredients include auxiliary binders which contribute to the ease of formation and general quality of the tablet. Auxiliary binders include starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

Also color additives can be used. Such color additives include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes adsorbed on aluminum hydroxide or other carriers.

Processing

The process steps of the present invention require the use of an uncured shearform matrix, that is, a shearform matrix which has not undergone significant recrystallization.

The preparation of floss suitable for practicing the present invention is disclosed in co-assigned U.S. Patents 5,380,473 and 5,429,836, both of which are incorporated by reference herein. Preferably the floss is a "shearform matrix" produced by subjecting a feedstock which contains a sugar carrier to flash-flow processing. For purposes of this invention, the term "shearform" will include flash-heat and flash-shear matrices and will be interchangeably used with the term "floss", which will include all amorphous material, regardless of shape, which is produced by the flash-heat and flash-shear processes.

One useful apparatus for implementing a flash-heat process is described in copending U.S. application Serial No. 08/854,344, filed May 12, 1997, entitled "Apparatus for Melt Spinning Feedstock Material having a Flow Restricting Ring".

Any other apparatus or physical process which provides similar forces and temperature gradient conditions can also be used.

The matrix particles are optionally treated with about 0.1 to about 5% of lactose and/or a crystallization modifier and chopped before other ingredients are added to them.

The tablet formulation is compacted/densified before the tableting operation. This pre-tableting compaction/densification step can be performed using any suitable methods which apply force against the shearform matrix and cause the added binding material to migrate internally into the network of floss particles and cause the matrix made from sugar alcohol-containing constituents to become less sticky.

In the initial compaction and densification steps, the tableting composition containing a binding material is subjected to uniform force, such that the resultant mass is substantially free of surface stickiness. A preferred means of performing this process is roller compaction. Machines useful in the invention include those referred to as "Chilsonator" or "Pharmapaktor". These and similar machines are designed to turn out a compacted mass in a steady, continuous flow at a high rate of speed.

Such a machine utilizes two grooved rollers revolving toward each other. The space between the rollers is controlled by hydraulic rams, so that the machine is capable of exerting known pressures on any solid material which flows between the rollers. The speed of rotation of the rollers is also regulated. The solid particulate material is fed between the rollers from a hopper. After passing through the rollers, the compacted mass

resembles a thin sheet, the surface of which is substantially free of stickiness.

The initial compaction and densification steps are not limited to use of the above techniques. Other suitable machinery and techniques are contemplated, provided they render the exposed floss surface free of stickiness.

The compaction processes can be performed at ambient temperature and humidity. Compaction forces may vary depending on the specific tablet formulation. Generally, forces up to about 5,000 psi are applied.

Once the tableting composition has been subjected to the compaction step, the compacted mass is sized to a desired particle size. The resultant particles are free flowing because their surfaces are substantially dry to the touch and do not exhibit the tackiness of the original uncompacted tableting composition. Sizing of the particles to obtain a uniform size further enhances the flowability of these particles. Mesh screens, milling and other such sizing techniques are useful. Mesh sizes may range from about 200 to about 1,500 .

Once granulates are formed, optional tableting aids can be incorporated into the tableting composition for use in making discrete dosage units. The once sticky uncompacted tableting composition has been thus transformed into free flowing particles. Conventional tableting equipment can be employed and discrete dosage units can be made using either low pressure or high pressure forces. Low pressure forces are typically under 500 psi. High pressure forces are usually above 500 psi and are generally in the range of 1,000 to 6,000 psi.

Using the present invention a strong, highly attractive tablet can be produced having a texture and internal structure which is relatively porousfor ease of solubilization. Moreover, the tablet is high in strength because of self-binding properties.

When chewable tablets are made, they are compressed to hardness values of about 3 to about 20 SCU's.

The following examples are intended to further illustrate the invention:

EXAMPLE I

A shearform matrix was prepared subjecting a blend of appropriate ingredients to flashflow processing using the device described in U.S. application Serial No.

08/854,344, filed May 12, 1997. The combination included a saccharide-based carrier material, a hydrophilic sugar alcohol and a surfactant. This blend contained:

Ingredient	Percentage
Sucrose	84.75
Sorbitol	15.00
Lactose	3.00
TWEEN™ 80 (surfactant)	0.25
	100

The ingredients were mixed, then subjected to flash-heat processing. The shearform matrix resulting from the processing was reduced in volume by chopping for less than a minute in a Stephan High shear mixer.

The shearform matrix of Example I was then combined with various additives.

EXAMPLE II

The shearform matrix of Example I was used in the following composition:

Ibuprofen Composition

Ingredient	Percentage
Shearform Matrix of Example I	47.18
Ibuprofen Microspheres	37.00
Flavors	7.42
Sweeteners	1.30
Glycerine	2.00
Starch	5.00
Color	0.10
	100.00

The glycerine and ibuprofen microspheres were mixed and added to one-fourth of the shearform matrix floss. These ingredients were then mixed in a Hobart mixer for about 1 minute. The remaining three portions of floss were added and mixed in intervals. The flavors, sweeteners and starch were sieved through 20 mesh, then added and mixed for an additional minute. Finally, the color was sieved to 20 mesh, added and mixed until the blend took on a homogeneous color.

The blend was then subjected to roller compaction sufficient to internalize the glycerine binder into the floss. The compacted mass was sized using a screen of

approximately 20 mesh and mixed again to yield free flowing granulates. The resultant flowable particulates were then tableted. The tablets integrity and friability were within specified limits.

EXAMPLE III

An uncured shearform floss was formed, using the process of Example I, from the following composition:

Ingredients	Percentage
Sucrose	84.75
Sorbitol 712	15.00
TWEEN 80	0.25

The following tableting composition was then formed using this floss.

Ingredient	Percentage
Floss	46.23
APAP Microspheres	48.85
Glycerine	3.00
Lemon Juice	0.25
Cream Flavor	0.25
Citric Acid Anhydrous	0.25
Cabosil	0.50
Aspartame	0.67
	100.00

The APAP microspheres and glycerine were first mixed for about 1 minute by hand. The floss was chopped and then added to the APAP/glycerine mix and all other ingredients, with mixing.

The resultant blend was then subjected to roller compaction and screened to a 20 mesh size. The resultant particles were free flowing and were easily processable in high speed tableting equipment to form tablets having initial hardness of about 1 lb. The tablets exhibited rapid dissolu-tion when placed in the mouth and excellent structural integ-rity to be handled and packaged without cracking or breaking.

Example IV

Chewable Calcium Carbonate with Vitamin D

A floss was made from the following formulation via a procedure similar to that of Example I.

I. Floss Formulation

Sucrose	78.25%
Sorbitol	11.0%
Xylitol	10.0%
Polysorbate 80	0.75%

The sucrose, sorbitol, xylitol, and Polysorbate 80 were blended in a Littleford FKM600 mixer for 10 minutes. The blend was then subjected to Shearform process at 60Hz and 250°C temperature using the 5" crown head disclosed in U.S.S.N. 08/854,344, filed May 12, 1997 to make floss particles. The floss was chopped in the Littleford FKM600 mixer with 2% lactose and treated with ethanol (4% of the floss). The floss was dried at 45°C for 90 minutes. The floss was then milled/sieved through a 20 mesh screen using a Fitzmill or Apexmill.

II. Tablet Formulation

Calcium Carbonate USP	45.45%
Vitamin D_3 100SD	0.18%
Floss	49.37%
N&A Lemon Flavor	.80%
Citric Acid	1.20%
Adipic Acid	1.00%
Syloid 244FP	1.00%
Magnesium Stearate	1.00%

The calcium carbonate was blended with Vitamin D_3 for 15 minutes at speed 1 in a Littleford FM130. The milled floss, flavor, and acids were added and blended further for 5 minutes. The flow agent was added and blended for additional 2 minutes. The magnesium stearate was added and blended for additional 3 minutes.

The blend was then roller compacted using an Alexanderwerk WP50 Roll Compactor/granulator, equipped with two vertically-opposed rolls fed by twin feed

screws. The roller speed was maintained at 8 rpm, feed screw speed at 20 rpm and the hydraulic pressure was varied from 25 to 90 bars. The compacted granules had a dual screen size of 1.0 and 2.0 mm. The roller compacted granules were compressed on a Kilian T200 rotary press at 20-30 lbs. hardness, 2.75g tablet weight, 19mm round concave or flat-faced tooling.

Thus, while there has been described what are presently believed to be the preferred embodiments of the present invention, other and further modification and changes can be made thereto without departing from the true spirit of the invention. It is intended to include all further and other modifications and changes which come within the true scope of the invention as set forth in the claims.

WE CLAIM:

1. A method of making a chewable tablet comprising the steps of:

   1) preparing a cohesive, free-flowing tabletable composition based upon a shearform matrix and containing at least one bio-affecting agent, at least one crystallization modifier, and employing at least one of: (a) a binding additive, and (b) a sugar alcohol ingredient;

   2) densifying and milling that composition; and

   3) compressing it to form tablets.

2. The method of claim 1 wherein said densifying of the composition of step (1) is achieved using a roller compaction machine.

3. The method of claim 1 wherein said milling step produces particles of about 200μ to about 1,500μ size.

4. The method of claim 1 wherein said shearform matrix contains a carrier selected from the group consisting of: monosaccharides, disaccharides, sugar alcohols, polydextrose, maltodextrin, oligo-saccharides and mixtures thereof.

5. The method of claim 1 wherein said binding additive (a) is glycerine, and it is used in amount of 0.5% to about 5.0%.

6. The method of claim 1 wherein said sugar alcohol ingredient (b) includes at least one of mannitol, sorbitol and xylitol.

7. The method of claim 6 wherein both (a) and (b) are used.

8. A chewable tablet made by the method of claim 7.

9. The method of claim 4 wherein the composition of step (1) is contacted with at least one glidant before step (2).

10. A chewable tablet made by the method of claim 9.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 98/17069

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/20 A23G3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K A23G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 667 147 A (FUISZ) 16 August 1995 see page 7, line 38 - line 41 see page 2, line 23 - line 25 see page 2, line 28 - line 38 ---	1,3-10 2
Y	US 5 370 878 A (HALLMARK PHARMACEUTICALS) 6 December 1994 see the whole document ---	2
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 1998	17/12/1998

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/17069

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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